

6/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13848581 BIOSIS NO.: 200200477402

Inhibitors of **STAT** function.

AUTHOR: McKinney Judi(a); Raimundo Brian C; Cushing Timothy D; Yoshimura Hiromitsu; Ohuchi Yutaka; Hiratake Akira; Fukushima Hiroshi

AUTHOR ADDRESS: (a)Mill Valley, CA**USA

JOURNAL: Official Gazette of the United States Patent and Trademark Office
Patents 1260 (5):pNo Pagination July 30, 2002

MEDIUM: e-file

ISSN: 0098-1133

DOCUMENT TYPE: Patent

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Compounds, compositions and methods that are useful in the treatment of immunoregulatory conditions and disorders are provided herein. In particular, the invention provides compounds which modulate the function of a Signal Transducer and Activator of Transcription (**STAT**) protein. The compounds are represented by the general formula: ##STR1## wherein Y, Ar, X, A₂, A₁, R₁ and R₂ are defined herein. The compounds are useful to treat, for example, allergic and inflammatory conditions and disorders.

Gambel, Phillip

4/7/36 (Item 4 from file: 155)
DIALOG(R)File 155: MEDLINE(R)
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10022493 21956576 PMID: 11960303

Peroxisome proliferator-activated receptor-gamma agonists inhibit experimental allergic encephalomyelitis by blocking IL-12 production, IL-12 signaling and Th1 differentiation.

Natarajan C; Bright J J

Division of Neuroimmunology, Department of Neurology, Vanderbilt University School of Medicine, Nashville, TN 37212, USA.

Genes and immunity (England) Apr 2002, 3 (2) p59-70, ISSN 1466-4879

Journal Code: 100953417

Contract/Grant No.: R01 NS42257-01A1; NS; NINDS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Peroxisome proliferator-activated receptor-gamma (PPARgamma) is a nuclear receptor transcription factor that regulates adipocyte differentiation and glucose homeostasis. PPARgamma agonists are potent therapeutic agents for the treatment of type 2 diabetes and obesity. PPARgamma agonists also prevent inflammation in animal models, suggesting their use for the treatment of human inflammatory diseases. Experimental allergic encephalomyelitis (EAE) is a Th1 cell-mediated inflammatory demyelinating disease model of multiple sclerosis (MS) and IL-12 plays a crucial role in the pathogenesis of EAE and MS. In this study we have examined the effect of PPARgamma agonists on the pathogenesis of EAE. In vivo treatment of SJL/J mice with PPARgamma agonists, 15-deoxydelta(12,14) prostaglandin J2 or Ciglitazone, decreased the duration and clinical severity of active immunization and adoptive transfer models of EAE. PPARgamma agonists inhibited EAE in association with a decrease in IL-12 production and differentiation of neural antigen-specific Th1 cells. In vitro treatment of activated T cells with PPARgamma agonists inhibited IL-12-induced activation of JAK-STAT signaling pathway and Th1 differentiation. These findings highlight the fact that PPARgamma agonists regulate central nervous system inflammation and demyelination by inhibiting IL-12 production, IL-12 signaling and Th1 differentiation in EAE.

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Record Date Completed: 20020517

4/7/34 (Item 2 from file: 155)
DIALOG(R)File 155: MEDLINE(R)
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14887323 22105178 PMID: 12110143

The paradigm of IL-6: from basic science to medicine.

Naka Tetsuji; Nishimoto Norihiro; Kishimoto Tadamitsu

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Arthritis research (England) 05 09 2002, 4 Suppl 3 pS233-42, ISSN

1465-9905 Journal Code: 100913255

Document type: Journal Article; Review; Review Literature

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

IL-6 is a pleiotropic cytokine with a wide range of biological activities

in immune regulation, hematopoiesis, inflammation, and oncogenesis. Its activities are shared by IL-6-related cytokines such as leukemia inhibitory factor and oncostatin M. The pleiotropy and redundancy of IL-6 functions have been identified by using a unique receptor system comprising two functional proteins: an IL-6 receptor (IL-6R) and gp130, the common signal transducer of cytokines related to IL-6. Signal transduction through gp130 is mediated by two pathways: the JAK-STAT (Janus family tyrosine kinase-signal transducer and activator of transcription) pathway and the Ras mitogen-activated protein kinase pathway. The negative regulators of IL-6 signaling have also been identified, although the physiological roles of the molecules are not yet fully understood. The pathological roles of IL-6 have also been clarified in various disease conditions, such as inflammatory, autoimmune, and malignant diseases. On the basis of the findings, a new therapeutic approach to block the IL-6 signal using humanized anti-IL-6R antibody for rheumatoid arthritis, Castleman's disease, and multiple myeloma has been attempted. (113 Refs.)

Record Date Created: 20020711

Record Date Completed: 20030522

4/7/31 (Item 10 from file: 73)

DIALOG(R)File 73:EMBASE

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06830427 EMBASE No: 1997112928

Lymphocyte activation in health and disease

Berridge M.J.

M.J. Berridge, Babraham Institute, Laboratory of Molecular Signalling, P. O. Box 158, Cambridge CB2 3ES United Kingdom

Critical Reviews in Immunology (CRIT. REV. IMMUNOL.) (United States) 1997, 17/2 (155-178)

CODEN: CCRID ISSN: 1040-8401

DOCUMENT TYPE: Journal; Review

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 155

Lymphocytes employ a complex assembly of signaling elements that have been organized on a spatiotemporal map to define their role in stimulating both proliferation and apoptosis. The antigen-major histocompatibility complex (MHC) initiates the sequence by organizing the assembly of an active T-cell receptor (TCR) complex responsible for transmitting information down various signaling cassettes (e.g., the IP_{inf} 3/Casup 2^{sup} +, DAG/PKC, ras/MAPK, and the PI 3-K pathways). It is proposed that CD28 may exert its costimulatory action by facilitating the assembly of an effective scaffold of signaling elements within the TCR complex. The absence of costimulation through CD28 seems to result in the assembly of a defective scaffold that reverses slowly and may thus account for the state of unresponsiveness responsible for peripheral T-cell tolerance. The signaling cassettes activated by the TCR and CD28 then engage cytosolic factors that transmit information into the nucleus to activate the genes that code for the IL-2 and Fas signaling pathways. The IL-2 and Fas receptors employ additional signaling cassettes (e.g., the JAK/STAT and the sphingomyelinase/ceramide pathways) to mediate their effects on proliferation and apoptosis, respectively. Information concerning these signaling systems is beginning to provide therapeutic strategies to manipulate the immune system to overcome human immunodeficiency virus (HIV) infection, autoimmune diseases, and graft rejection.

4/7/29 (Item 8 from file: 73)

DIALOG(R)File 73:EMBASE

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07355012 EMBASE No: 1998265827

Chimeric receptors for Jak-Stat signal transduction

Expert Opinion on Therapeutic Patents (EXPERT OPIN. THER. PAT.) (United Kingdom) 1998, 8/8 (1057-1059)
CODEN: EOTPE ISSN: 1354-3776
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 5

This patent describes a method whereby cell responses may be manipulated through the use of chimeric cytokine or growth factor receptors. The chimeric receptors comprise extracellular domains attached to an intracellular domain containing signalling components of the Jak/Stat pathway. It has been demonstrated that replacement of the extracellular domain of the interferon gamma (IFNgamma) receptor subunits with the extracellular domain of another cytokine or growth factor receptor such as EPO reproduces IFNgamma specific signal transduction resulting in expression of MHC class I. In addition, the extracellular domain may be replaced by immunoglobulin antigen binding domains or the cytokine/growth factor ligand itself to facilitate specific cell-signalling. It is envisioned that introduction of such chimeric cytokine/growth factor receptors into specific cells (including T-cells, natural killer cells and macrophages) may provide a specific therapeutic opportunity for the treatment of many cancers, autoimmune diseases, inflammatory diseases and for viral infections.

4/7/24 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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11432702 EMBASE No: 2002004801
Putting the brakes on arthritis: Can suppressors of cytokine signaling (SOCS) suppress rheumatoid arthritis?
Rottapel R.
R. Rottapel, Department of Immunology, University of Toronto, Ontario Cancer Institute, 610 University Avenue, Toronto, Ont. M5G 2M9 Canada
AUTHOR EMAIL: rottapel@uhnres.utoronto.ca
Journal of Clinical Investigation (J. CLIN. INVEST.) (United States)
2001, 108/12 (1745-1747)
CODEN: JCINA ISSN: 0021-9738
DOCUMENT TYPE: Journal ; Note
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 24

4/7/22 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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12193252 EMBASE No: 2003304185
Negative regulation of cytokine signaling and inflammatory diseases
Inagaki-Ohara K.; Hanada T.; Yoshimura A.
A. Yoshimura, Div. of Molec./Cellular Immunology, Medical Institute of Bioregulation, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812-8582 Japan
AUTHOR EMAIL: yakihiko@bioreg.kyushu-u.ac.jp
Current Opinion in Pharmacology (CURR. OPIN. PHARMACOL.) (United Kingdom) 2003, 3/4 (435-442)
CODEN: COPUB ISSN: 1471-4892
PUBLISHER ITEM IDENTIFIER: S1471489203000705
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 90

Immune and inflammatory systems are controlled by multiple cytokines, including interleukins and interferons. These cytokines exert their biological functions through Janus tyrosine kinases and signal transducer and activators of transcription (STATs). The cytokine-inducible SH2 proteins (CIS) and suppressors of cytokine signaling (SOCS) are a family of intracellular proteins, several of which have emerged as key physiological regulators of cytokine responses, including those that regulate the inflammatory system. Several recent advances have been made in this field, including treatment of inflammatory diseases by modulating extracellular and intracellular signaling pathways.

stat3

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14342399 BIOSIS NO.: 200300336428

Role of Signal Transducer and Activation of Transcription 3 (STAT-3) in Immune Tolerance: Blockade of Stat3 Signaling in Antigen-Presenting Cells (APCs) Breaks Antigen-Specific T-Cell Anergy.

AUTHOR: Cheng Fengdong(a); Cuenca Alex G(a); Wang Hongwei(a); Huang Mei(a); Schoenberger Stephen(a); Yu Hua(a); Jove Rich(a); Sotomayor Eduardo M(a)

AUTHOR ADDRESS: (a)Interdisciplinary Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA**USA

JOURNAL: Blood 100 (11):pAbstract No 35 November 16 2002 2002

MEDIUM: print

CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002

SPONSOR: American Society of Hematology

ISSN: 0006-4971

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: APCs play an important role in the initiation of antigen-specific T-cell responses. The demonstration however, that these cells are also required for the induction of T-cell tolerance, places APCs at the center of a critical decision leading to immune activation versus immune tolerance. Although the state of activation and/or differentiation of the APC has been proposed to be the central determinant of T-cell priming versus unresponsiveness, the intracellular pathway(s) involved in this critical decision remain to be elucidated. Recent studies have shown that Stat3 signaling pathway may negatively regulate inflammatory responses. To assess therefore whether Stat3 signaling in APCs may influence antigen-specific T-cell responses, we treated peritoneal elicited macrophages (PEM) with the tyrosine kinase inhibitor, tyrphostin AG490, a compound known to block Stat3 activation. AG490-treated PEM display an enhanced presentation of HA-peptide to naive CD4+ T cells specific for a MHC class II restricted epitope of influenza hemagglutinin (HA), as determined by the ability of these clonotypic T-cells to proliferate and produce higher levels of IL-2 and IFN-gamma as compared to T cells encountering HA-peptide on untreated or LPS-treated PEM. More importantly, tolerized CD4+ T-cells (isolated from tumor bearing mice) exposed to AG490-treated APCs, recover their ability to proliferate and to produce cytokines in response to cognate antigen stimulation. In sharp contrast, tolerized T cells encountering antigen presented by untreated APCs remained fully unresponsive. This enhancement in APCs function correlated with inhibition of STAT3 DNA-binding activity and was observed in both PEM as well as dendritic cells treated with AG490. Conversely, APCs with increased Stat3 activity (i.e. PEM treated with IL-10 or transiently transfected with constitutively activated Stat3c) were impaired in their antigen presenting capabilities leading to significantly diminished antigen-specific T-cell responses. To confirm

these results, we evaluated the antigen-presenting capabilities of PEM from mice with a cell type-specific disruption of the Stat3 gene. In response to LPS-stimulation, Stat3-/ PEM not only fully prime naive antigen-specific T-cells, but also restore the responsiveness of anergic CD4+ T-cells. Stat3-/ PEM display an activated phenotype (increased expression of MHC class II and co-stimulatory molecules B7.1, B7.2 and B7-DC). Furthermore, utilizing multi-template RNA probes we found that LPS-treated Stat3-/ PEMs display higher mRNA levels of the pro-inflammatory mediators IL-12, MIP-1alpha, MIP1-beta, IP-10, RANTES, but not IL-10. Neutralization experiments with anti-IL-12 and anti-RANTES antibodies points to these pro-inflammatory mediators as playing a critical role in the ability of Stat3-/ PEM to break T-cell anergy.

Taken together, our results establish a novel role for STAT3 signaling in APCs function and regulation of T-cell responses. provide a molecular target to regulate immune activation versus immune tolerance, a critical decision with profound implications in autoimmunity, transplantation and cancer immunotherapy.

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Set      Items    Description
S1       135     STAT AND AUTOIMMUN?
S2       86      RD S1 (unique items)
S3       53      S2 AND (VIVO OR THERAP? OR TREAT? OR PREVENT?)
S4       53      RD S3 (unique items)
S5       35      STAT AND ALLERGY AND (VIVO OR THERAP? OR TREAT? OR PREVENT-
          ?)
S6       32      RD S5 (unique items)
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Set      Items    Description
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S2       86      RD S1 (unique items)
S3       53      S2 AND (VIVO OR THERAP? OR TREAT? OR PREVENT?)
S4       53      RD S3 (unique items)
S5       35      STAT AND ALLERGY AND (VIVO OR THERAP? OR TREAT? OR PREVENT-
          ?)
S6       32      RD S5 (unique items)
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Gambel, Phillip

To: STIC-ILL
Subject: stat and autoimmunity and allergy

stic

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308-3997

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4/7/36 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10022493 21956576 PMID: 11960303

Peroxisome proliferator-activated receptor-gamma agonists inhibit experimental allergic encephalomyelitis by blocking IL-12 production, IL-12 signaling and Th1 differentiation.

Natarajan C; Bright J J

Division of Neuroimmunology, Department of Neurology, Vanderbilt University School of Medicine, Nashville, TN 37212, USA.

Genes and immunity (England) Apr 2002, 3 (2) p59-70, ISSN 1466-4879
Journal Code: 100953417

Contract/Grant No.: R01 NS42257-01A1; NS; NINDS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Peroxisome proliferator-activated receptor-gamma (PPARgamma) is a nuclear receptor transcription factor that regulates adipocyte differentiation and glucose homeostasis. PPARgamma agonists are potent therapeutic agents for the treatment of type 2 diabetes and obesity. PPARgamma agonists also prevent inflammation in animal models, suggesting their use for the treatment of human inflammatory diseases. Experimental allergic encephalomyelitis (EAE) is a Th1 cell-mediated inflammatory demyelinating disease model of multiple sclerosis (MS) and IL-12 plays a crucial role in the pathogenesis of EAE and MS. In this study we have examined the effect of PPARgamma agonists on the pathogenesis of EAE. In vivo treatment of SJL/J mice with PPARgamma agonists, 15-deoxydelta(12,14) prostaglandin J2 or Ciglitazone, decreased the duration and clinical severity of active immunization and adoptive transfer models of EAE.

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4/7/34 (Item 2 from file: 155)
DIALOG(R)File 155: MEDLINE(R)
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14887323 22105178 PMID: 12110143

The paradigm of IL-6: from basic science to medicine.

Naka Tetsuji; Nishimoto Norihiro; Kishimoto Tadamitsu

Department of Molecular Medicine, Osaka University Graduate School of Medicine, Japan. naka@imed3.med.osaka-u.ac.jp

Arthritis research (England) 05 09 2002, 4 Suppl 3 pS233-42, ISSN

1465-9905 Journal Code: 100913255

Document type: Journal Article; Review; Review Literature

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

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Record Date Completed: 20030522

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4/7/31 (Item 10 from file: 73)
DIALOG(R)File 73: EMBASE
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06830427 EMBASE No: 1997112928

Lymphocyte activation in health and disease

Berridge M.J.

M.J. Berridge, Babraham Institute, Laboratory of Molecular Signalling, P.

O. Box 158, Cambridge CB2 3ES United Kingdom

Critical Reviews in Immunology (CRIT. REV. IMMUNOL.) (United States)

1997, 17/2 (155-178)

CODEN: CCRID ISSN: 1040-8401

DOCUMENT TYPE: Journal; Review

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 155

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information down various signaling cassettes (e.g., the IPinf 3/Casup 2sup +, DAG/PKC, ras/MAPK, and the PI 3-K pathways). It is proposed that CD28 may exert its costimulatory action by facilitating the assembly of an effective scaffold of signaling elements within the TCR complex. The absence of costimulation through CD28 seems to result in the assembly of a defective scaffold that reverses slowly and may thus account for the state of unresponsiveness responsible for peripheral T-cell tolerance. The signaling cassettes activated by the TCR and CD28 then engage cytosolic factors that transmit information into the nucleus to activate the genes that code for the IL-2 and Fas signaling pathways. The IL-2 and Fas receptors employ additional signaling cassettes (e.g., the JAK/STAT and the sphingomyelinase/ceramide pathways) to mediate their effects on proliferation and apoptosis, respectively. Information concerning these signaling systems is beginning to provide therapeutic strategies to manipulate the immune system to overcome human immunodeficiency virus (HIV) infection, autoimmune diseases, and graft rejection.

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4/7/29 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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07355012 EMBASE No: 1998265827
Chimeric receptors for Jak-Stat signal transduction
Expert Opinion on Therapeutic Patents (EXPERT OPIN. THER. PAT.) (United Kingdom) 1998, 8/8 (1057-1059)
CODEN: EOTPE ISSN: 1354-3776
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 5

This patent describes a method whereby cell responses may be manipulated through the use of chimeric cytokine or growth factor receptors. The chimeric receptors comprise extracellular domains attached to an intracellular domain containing signalling components of the Jak/Stat pathway. It has been demonstrated that replacement of the extracellular domain of the interferon gamma (IFNgamma) receptor subunits with the extracellular domain of another cytokine or growth factor receptor such as EPO reproduces IFNgamma specific signal transduction resulting in expression of MHC class I. In addition, the extracellular domain may be replaced by immunoglobulin antigen binding domains or the cytokine/growth factor ligand itself to facilitate specific cell-signalling. It is envisioned that introduction of such chimeric cytokine/growth factor receptors into specific cells (including T-cells, natural killer cells and macrophages) may provide a specific therapeutic opportunity for the treatment of many cancers, autoimmune diseases, inflammatory diseases and for viral infections.

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4/7/24 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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11432702 EMBASE No: 2002004801
Putting the brakes on arthritis: Can suppressors of cytokine signaling (SOCS) suppress rheumatoid arthritis?
Rottapell R.
R. Rottapell, Department of Immunology, University of Toronto, Ontario Cancer Institute, 610 University Avenue, Toronto, Ont. M5G 2M9 Canada
AUTHOR EMAIL: rottapel@uhnres.utoronto.ca
Journal of Clinical Investigation (J. CLIN. INVEST.) (United States)
2001, 108/12 (1745-1747)

CODEN: JCINA ISSN: 0021-9738
DOCUMENT TYPE: Journal ; Note
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 24

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4/7/22 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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12193252 EMBASE No: 2003304185
Negative regulation of cytokine signaling and inflammatory diseases
Inagaki-Ohara K.; Hanada T.; Yoshimura A.
A. Yoshimura, Div. of Molec./Cellular Immunology, Medical Institute of
Bioregulation, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812-8582
Japan
AUTHOR EMAIL: yakihiko@bioreg.kyushu-u.ac.jp
Current Opinion in Pharmacology (CURR. OPIN. PHARMACOL.) (United
Kingdom) 2003, 3/4 (435-442)
CODEN: COPUB ISSN: 1471-4892
PUBLISHER ITEM IDENTIFIER: S1471489203000705
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 90

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stat3-----stat-----

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14342399 BIOSIS NO.: 200300336428
Role of Signal Transducer and Activation of Transcription 3 (STAT-3)
in Immune Tolerance: Blockade of Stat3 Signaling in Antigen-Presenting
Cells (APCs) Breaks Antigen-Specific T-Cell Anergy.
AUTHOR: Cheng Fengdong(a); Cuenca Alex G(a); Wang Hongwei(a); Huang Mei(a);
Schoenberger Stephen(a); Yu Hua(a); Jove Rich(a); Sotomayor Eduardo M(a)
AUTHOR ADDRESS: (a)Interdisciplinary Oncology, H. Lee Moffitt Cancer
Center, Tampa, FL, USA**USA
JOURNAL: Blood 100 (11):pAbstract No 35 November 16 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of
Hematology Philadelphia, PA, USA December 06-10, 2002
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: APCs play an important role in the initiation of antigen-specific

T-cell responses. The demonstration however, that these cells are also required for the induction of T-cell tolerance, places APCs at the center of a critical decision leading to immune activation versus immune tolerance. Although the state of activation and/or differentiation of the APC has been proposed to be the central determinant of T-cell priming versus unresponsiveness, the intracellular pathway(s) involved in this critical decision remain to be elucidated. Recent studies have shown that Stat3 signaling pathway may negatively regulate inflammatory responses. To assess therefore whether Stat3 signaling in APCs may influence antigen-specific T-cell responses, we treated peritoneal elicited macrophages (PEM) with the tyrosine kinase inhibitor, tyrphostin AG490, a compound known to block Stat3 activation. AG490-treated PEM display an enhanced presentation of HA-peptide to naive CD4+ T cells specific for a MHC class II restricted epitope of influenza hemagglutinin (HA), as determined by the ability of these clonotypic T-cells to proliferate and produce higher levels of IL-2 and IFN-gamma as compared to T cells encountering HA-peptide on untreated or LPS-treated PEM. More importantly, tolerized CD4+ T-cells (isolated from tumor bearing mice) exposed to AG490-treated APCs, recover their ability to proliferate and to produce cytokines in response to cognate antigen stimulation. In sharp contrast, tolerized T cells encountering antigen presented by untreated APCs remained fully unresponsive. This enhancement in APCs function correlated with inhibition of STAT3 DNA-binding activity and was observed in both PEM as well as dendritic cells treated with AG490. Conversely, APCs with increased Stat3 activity (i.e. PEM treated with IL-10 or transiently transfected with constitutively activated Stat3c) were impaired in their antigen presenting capabilities leading to significantly diminished antigen-specific T-cell responses. To confirm these results, we evaluated the antigen-presenting capabilities of PEM from mice with a cell type-specific disruption of the Stat3 gene. In response to LPS-stimulation, Stat3-/ PEM not only fully prime naive antigen-specific T-cells, but also restore the responsiveness of anergic CD4+ T-cells. Stat3-/ PEM display an activated phenotype (increased expression of MHC class II and co-stimulatory molecules B7.1, B7.2 and B7-DC). Furthermore, utilizing multi-template RNA probes we found that LPS-treated Stat3-/ PEMs display higher mRNA levels of the pro-inflammatory mediators IL-12, MIP-1alpha, MIP1-beta, IP-10, RANTES, but not IL-10. Neutralization experiments with anti-IL-12 and anti-RANTES antibodies points to these pro-inflammatory mediators as playing a critical role in the ability of Stat3-/ PEM to break T-cell anergy. Taken together, our results establish a novel role for STAT3 signaling in APCs function and regulation of T-cell responses. provide a molecular target to regulate immune activation versus immune tolerance, a critical decision with profound implications in autoimmunity, transplantation and cancer immunotherapy.

-----stat-----

14409508 BIOSIS NO.: 200300403537

Redirection of B cell responsiveness by transforming growth factor beta receptor.

AUTHOR: Roes Jurgen(a); Choi B Ken; Cazac Balthazar B

AUTHOR ADDRESS: (a)Department of Immunology and Molecular Pathology, Windeyer Institute of Medical Sciences, University College London, 46 Cleveland Street, London, W1T 4JF, UK**UK E-Mail: j.roes@ucl.ac.uk

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 100 (12):p7241-7246 June 10 2003 2003

MEDIUM: print

ISSN: 0027-8424

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The multifunctional transforming growth factor beta receptor (TbetaR) ligand pair plays a central role in the regulation of lymphocyte homeostasis and prevention of autoimmunity. Although the mechanisms underlying the induction of transcriptional modulators by TbetaR have been studied in considerable detail, relatively little is known about the regulatory pathways targeted. To shed light on the mechanisms involved in negative regulation of B cell responses we identified TbetaR-dependent transcriptome changes by comparative gene expression profiling of normal and TbetaR-deficient primary B cells. The data reveal TbetaR-mediated induction of inhibitors of antigen receptor signaling (Ship-1, CD72) as well as inhibitors of the Jak/Stat pathway and signaling by means of Toll-like receptors (SOCS1,3). These inhibitory effects are complemented by induction of antiproliferative transcription factors. In contrast to this inhibition, G protein-coupled receptors such as CXCR4 and agonists mediating Ca²⁺ flux (inositol trisphosphate receptor subtype 2) are induced by TbetaR, indicating enhancement of the Ca²⁺ storage/release system and chemotactic responses. Suppression of proapoptotic genes suggests support of cell survival. Confirming the shift in B cell responsiveness, antigen-receptor-mediated activation of Syk and phospholipase C-gamma2, as well as Stat6 phosphorylation, is inhibited, whereas chemotaxis, Ca²⁺ release, and cell survival are enhanced in transforming growth factor-beta-sensitive B cells. The data provide a molecular basis for TbetaR-mediated inhibition of B cell responsiveness and indicate that TbetaR maintains homeostasis not only through inhibition of the cell cycle but also by delivering a coherent instructive signal that redirects responsiveness to microenvironmental cues.

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Regulation of T helper type 2 cell immunity by interleukin-4 and interleukin-13
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Type 2 cytokine responses are typical of immune reactions to parasitic helminth infections, allergies, and asthma, and are characterised by the production of the cytokines interleukin (IL)-4, IL-5, IL-9, and IL-13 by subsets of T helper type 2 (Th2) cells. These cytokines form a complex network of molecular and cellular interactions that mediate protective immunity to worm infection, but also induce inappropriate inflammatory responses to allergic challenge. Although considerable attention has been given to the roles played by IL-4 in Th2 responses, the identification of the related cytokine IL-13 has led to a re-evaluation of how these two molecules combine in the generation of Th2 immunity. Recent reports have highlighted that in certain challenges, IL-4 and IL-13 act in combination to ensure the rapid onset of a Th2-like response. However, these studies have also identified specific responses that are attributable to the

individual cytokines. For example, IL-13 appears to play a more dominant role than IL-4 in the expulsion of certain gastrointestinal parasites. In contrast, following schistosome infection, IL-13 induces a detrimental hepatic fibrosis, while IL-4 protects against endotoxemia. These results emphasise the complexity of the cytokine network, and highlight the care that needs to be taken when designing therapeutic intervention. (c) 2000 Elsevier Science Inc.

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The role of transcription factors in allergic inflammation
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The induction of allergic inflammation and the expression of allergic disorders are dependent on the coordinated regulation of numerous genes. The products of these genes determine lymphocyte phenotype, immunologic responsiveness, eosinophil and mast cell development, activation, migration and life span, adhesion molecule expression, cytokine synthesis, cell-surface receptor display, and processes governing fibrosis and tissue repair. Although the expression of gene products involved in these processes is regulated at multiple levels (eg, transcription, mRNA processing, translation, phosphorylation, and degradation), transcription represents an essential and often the most important determinant of their contribution to cellular function. Signal-dependent and cell type-specific regulation of gene expression is generally achieved by means of combinatorial interactions between sequence-specific transcription factors that recruit chromatin remodeling machinery and general transcription factors to promoter and enhancer regions of RNA polymerase II-dependent genes. As targets of signal-transduction pathways, transcription factors integrate the response of the cell to the myriad of inputs it receives. This integration can be accomplished by the effect of signaling cascades on the activation status or subcellular locus of transcription factors or by transcription factor dimerization induced by means of ligand binding. This review will identify the major families of transcription factors important in allergic mechanisms and discuss their interactions, their mechanisms of action, and their interrelated and competitive actions, as well as implications for therapy of allergic disorders.

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